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09/917,154	07/27/2001	Sean D. Monahan	Mirus.013.04.03	5474

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EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	12

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/917,154	Monahan et al.
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 5, 2003*

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above, claim(s) *19 and 20* is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

1. Claims 1-20 are pending. Claims 19 and 20 are withdrawn from examination since they are drawn to a non-elected invention.

2. The rejection of claims 5, 16 and 17 which were rejected under 35 U.S.C. 112, second paragraph has been overcome by amendment and the rejection is withdrawn.

3. Claims 8-15 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-14 of U.S. Patent No. 6,379,966. Applicants have indicated that a terminal disclaimer will be filed upon allowance of the claims.

4. Claims 1-7 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 9, 11 and 12 of copending Application No. 09/391,260. Applicants have indicated that a terminal disclaimer will be filed upon allowance of the claims.

5. Claims 1-7, 17 and 18 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 20 and 22 of copending Application No. 09/447,966. Applicants have indicated that a terminal disclaimer will be filed upon allowance of the claims.

6. Claims 1-7 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 and 37-39 of

copending Application No. 09/707,000. Applicants have indicated that a terminal disclaimer will be filed upon allowance of the claims.

7. Claims 1-5, 7-13, 15 stand 17 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,328,470 (Nabel et al., (A)).

8. Claims 1-5, 7-13, 15 and 17 stand rejected under 35 U.S.C. 102(e) as being anticipated by US 5,698,531 (Nabel et al., (B)).

9. Claims 1-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over each of US 5,328,470 (Nabel et al., (A)) and US 5,698,531 (Nabel et al., (B)) in view of US 5,026,558 (Hwang).

Response to Arguments

Priority

10. This statement is repeated from the previous office action.

11. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 08/571,536, filed December 13, 1995. A reference to the US patent issued from Application No. 08/571,536 is set forth in the priority claim filed on October 8, 2001, however, the application number has not been mentioned. **A reference to the prior *application* must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the**

prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). (emphasis added) The amendment to the first line of the specification in Paper No. 11, filed May 5, 2003 does not include the Application No. 08/571,536, filed December 13, 1995.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Priority for the independent claims 1 and 8 is supported in US Application No. 08/571,536.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 8-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-14 of U.S. Patent No. 6,379,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because independent claims 1 and 11 of US 6,379,966 are a sub-genus of the instant claim 8. The

dependent claims 2-10 and 12-13 of US 6,379,966 repeat the claimed subject matter of the instant dependent claims 9-15.

14. Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 9, 11 and 12 of copending Application No. 09/391,260. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-7 are generic to the sub-genus of claims 7, 9, 11 and 12 of copending Application No. 09/391,260.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-7, 17 and 18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 20 and 22 of copending Application No. 09/447,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-7 are generic to the sub-genus of claims 19, 20 and 22 of copending Application No. 09/447,966.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 and 37-39 of copending Application No. 09/707,000. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-7 are generic to the sub-genus of claims 1-15 and 37-39 of copending Application No. 09/707,000.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

18. Claims 1-5, 7-13, 15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,328,470 (Nabel et al., (A)).

Nabel et al. ('470) teach at the abstract, column 4, line 43 bridging to column 5, line 49, column 7, lines 19-51, column 8, lines 32-35, and lines 51-68, column 12, line 62 bridging to column 15, line 4, a process for delivering a polynucleotide into an extravascular parenchymal cell of a mammal by inserting the polynucleotide into a mammalian blood vessel in-vivo, increasing the permeability of the blood vessel, passing the polynucleotide in a solution through the blood vessel into the extravascular space, thereby delivering the polynucleotide into an extravascular parenchymal cell, and then expressing the polynucleotide. The permeability of the blood vessel is increased with pressure against the blood vessel walls, which may be done by increasing the volume of the fluid in the blood vessel. The time of residence of the polynucleotide-containing solution in the blood vessel and pressure are variable. Various tissues may be treated by this process, including the liver (hepatocytes). Instant claim 8 recites that the polynucleotide alone has a more negative zeta potential than a polynucleotide-compound complex. Polynucleotides are well known to those of ordinary skill in the art to have a negative zeta potential. The polynucleotide-liposome complex taught by Nabel et al. ('470) is known to have a less negative zeta potential than the polynucleotide alone. Nabel et al. ('470) teach at column 13, line 53 - column 14, line 68, the combination of DNA-liposome complexes with agents such as poly-L-lysine or polybrene, which increase the zeta potential negativity of the complex. Therefore, the teachings of Nabel et al. ('470) anticipate the instant claimed invention.

Response to Arguments

19. Arguments presented in Paper No. 11 at page 5 assert that Nabel et al. ('470) does not provide guidance or teachings on delivery of nucleic acid to cells outside of a blood vessel, (non-vascular cells).

Nabel et al. ('470) teach at column 8, lines 53-61 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of a organ or tissue cells may be accomplished by one of two methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells). The argument is therefore not convincing.

20. Arguments presented in Paper No. 11 at page 6 assert that Nabel et al. ('470) makes no distinction between high pressure which results in delivery of a nucleic acid to cells of a blood vessel wall, and high pressure which results in delivery of nucleic acids to cells outside of the blood vessel, and that no evidence is provided of delivery of a nucleic acid to cells outside of a blood vessel. The assertion is made that since no evidence is presented to show delivery of nucleic acid to cells outside of a blood vessel, there is therefore, no support for this statement made by Nabel et al. ('470).

While it is true that there is no specific guidance on the numerical or physical bounds of what is meant by "high pressure", the lack of information does not preclude, nor negative the statement that nucleic acid may be delivered to cells outside of the blood vessel. Likewise, since

there are no specific examples of delivery of nucleic acid to cells outside of the blood vessel, this does not negative the statement that nucleic acids may be delivered to cells outside of a blood vessel. The instant specification at examples 1-4 provide information on delivery which does not include specifics on pressures used for delivery of nucleic acids to cells outside of a blood vessel. Further, the instant specification does not provide specific guidance on pressures required for delivery of nucleic acids to cells outside of a blood vessel. In view of these facts, the assertion is not found convincing.

21. Arguments presented in Paper No. 11 at page 6 assert that quotations from the inventors of Nabel et al. ('470) patent (various sources) teach that cells of blood vessel walls were transfected by high pressure delivery of a nucleic acid, and that the quotations do not teach the transfection of cells outside of the blood vessel walls.

The quotations do not directly discuss the teachings of the Nabel et al. ('470) patent regarding delivery of nucleic acids to cells outside of a blood vessel wall, nor do the quotations provide any basis to repudiate the teachings of the Nabel et al. ('470) patent regarding the delivery of nucleic acids to cells outside of a blood vessel wall. The argument is therefore not found convincing.

22. Arguments presented in Paper No. 11 at pages 6-7 assert that the method of Nabel et al. ('470) fails to achieve delivery of nucleic acids to extravascular parenchymal cells. As evidence of this assertion, a quotation is made from Paper No. 5 from the file history of Nabel et al. ('531).

The quotations do not directly discuss the teachings of the Nabel et al. ('470) patent regarding delivery of nucleic acids to cells outside of a blood vessel wall, nor do the quotations provide any basis to repudiate the teachings of the Nabel et al. ('470) patent regarding the delivery of nucleic acids to cells outside of a blood vessel wall. The argument is therefore not found convincing.

23. Arguments presented in Paper No. 11 at page 7 assert that Nabel et al. ('470) provides no direction on delivery to cells other than endothelial cells and smooth muscle cells located in a very small, defined region of a blood vessel. DNA is not delivered directly to parenchymal cells. It is further asserted that only general background statements suggest delivery of nucleic acid to parenchymal cells.

Nabel et al. ('470) teach at column 8, lines 53-61 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of organ or tissue cells may be accomplished by one of two methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells). The argument is therefore not convincing.

24. Arguments presented in Paper No. 11 at page 7 assert that Nabel et al. ('470) provides no teaching on delivery to cells other than endothelial cells and smooth muscle cells located in a very small, defined region of a blood vessel. The "tossing out of a mere germ of an idea does not

constitute a teaching", and Nabel ('470) does not teach how to deliver a polymer complex to an extravascular cell.

Nabel et al. ('470) teach at column 5, lines 14-16 "vector DNA may be delivered to a large amount of parenchymal tissue distributed through the capillary circulation." Nabel et al. ('470) teach at column 7, lines 36-41 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of a organ or tissue cells may be accomplished by one of two methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells). The argument is therefore not convincing.

25. Claims 1-5, 7-13, 15 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,698,531 (Nabel et al., (B)).

Nabel et al. (B) teach at the abstract, column 3, line 52 bridging to column 4, line 24, column 5, line 54 bridging to column, column 7, line 50, column 9, lines 57-67, column 10, lines 41-53, and column 11, lines 19-37, a process for delivering a polynucleotide into an extravascular parenchymal cell of a mammal by inserting the polynucleotide into a mammalian blood vessel in-vivo, increasing the permeability of the blood vessel, passing the polynucleotide in a solution through the blood vessel into the extravascular space, thereby delivering the polynucleotide into an extravascular parenchymal cell, and then expressing the polynucleotide.

The permeability of the blood vessel is increased with pressure against the blood vessel walls, which may be done by increasing the volume of the fluid in the blood vessel. The time of residence of the polynucleotide-containing solution in the blood vessel and pressure are variable. Various tissues may be treated by this process, including the liver (hepatocytes). Instant claim 8 recites that the polynucleotide alone has a more negative zeta potential than a polynucleotide-compound complex. Polynucleotides are well known to those of ordinary skill in the art to have a negative zeta potential. The polynucleotide-liposome complex taught by Nabel et al. (B) is known to have a less negative zeta potential than the polynucleotide alone. Nabel et al. ('531) teach at column 13, lines 1-28, the combination of DNA-liposome complexes with agents such as poly-L-lysine or polybrene, which increase the zeta potential negativity of the complex. Therefore, the teachings of Nabel et al. (B) anticipate the instant claimed invention.

Response to Arguments

26. Arguments presented in Paper No. 11 at page 5 assert that Nabel et al. ('531) does not provide guidance or teachings on delivery of nucleic acid to cells outside of a blood vessel, (non-vascular cells).

Nabel et al. ('531) teach at column 4, lines 16-18 "vector DNA may be delivered to a large amount of parenchymal tissue distributed through the capillary circulation." Nabel et al. ('531) teach at column 7, lines 36-41 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of organ or tissue cells may be accomplished by one of two

methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells). The argument is therefore not convincing.

27. Arguments presented in Paper No. 11 at page 6 assert that Nabel et al. ('531) makes no distinction between high pressure which results in delivery of a nucleic acid to cells of a blood vessel wall, and high pressure which results in delivery of nucleic acids to cells outside of the blood vessel, and that no evidence is provided of delivery of a nucleic acid to cells outside of a blood vessel. The assertion is made that since no evidence is presented to show delivery of nucleic acid to cells outside of a blood vessel, there is therefore, no support for this statement made by Nabel et al. ('531).

While it is true that there is no specific guidance on the numerical or physical bounds of what is meant by "high pressure", the lack of information does not preclude, nor negative the statement that nucleic acid may be delivered to cells outside of the blood vessel. Likewise, since there are no specific examples of delivery of nucleic acid to cells outside of the blood vessel, this does not negative the statement that nucleic acids may be delivered to cells outside of a blood vessel. The instant specification at examples 1-4 provide information on delivery which does not include specifics on pressures used for delivery of nucleic acids to cells outside of a blood vessel. Further, the instant specification does not provide specific guidance on pressures required for

delivery of nucleic acids to cells outside of a blood vessel. In view of these facts, the assertion is not found convincing.

28. Arguments presented in Paper No. 11 at page 6 assert that quotations from the inventors of Nabel et al. ('531) patent (various sources) teach that cells of blood vessel walls were transfected by high pressure delivery of a nucleic acid, and that the quotations do not teach the transfection of cells outside of the blood vessel walls.

The quotations do not directly discuss the teachings of the Nabel et al. ('531) patent regarding delivery of nucleic acids to cells outside of a blood vessel wall, nor do the quotations provide any basis to repudiate the teachings of the Nabel et al. ('531) patent regarding the delivery of nucleic acids to cells outside of a blood vessel wall. The argument is therefore not found convincing.

29. Arguments presented in Paper No. 11 at pages 6-7 assert that the method of Nabel et al. ('531) fails to achieve delivery of nucleic acids to extravascular parenchymal cells. As evidence of this assertion, a quotation is made from Paper No. 5 from the file history of Nabel et al. ('531).

The quotations do not directly discuss the teachings of the Nabel et al. ('531) patent regarding delivery of nucleic acids to cells outside of a blood vessel wall, nor do the quotations provide any basis to repudiate the teachings of the Nabel et al. ('531) patent regarding the delivery of nucleic acids to cells outside of a blood vessel wall. The argument is therefore not found convincing.

30. Arguments presented in Paper No. 11 at page 7 assert that Nabel et al. ('531) provides no direction on delivery to cells other than endothelial cells and smooth muscle cells located in a very small, defined region of a blood vessel. DNA is not delivered directly to parenchymal cells. It is further asserted that only general background statements suggest delivery of nucleic acid to parenchymal cells.

Nabel et al. ('531) teach at column 8, lines 53-61 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of a organ or tissue cells may be accomplished by one of two methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells). The argument is therefore not convincing.

31. Arguments presented in Paper No. 11 at page 7 assert that Nabel et al. ('531) provides no teaching on delivery to cells other than endothelial cells and smooth muscle cells located in a very small, defined region of a blood vessel. The "tossing out of a mere germ of an idea does not constitute a teaching", and Nabel ('531) does not teach how to deliver a polymer complex to an extravascular cell.

Nabel et al. ('531) teach at column 4, lines 16-18 "vector DNA may be delivered to a large amount of parenchymal tissue distributed through the capillary circulation." Nabel et al. ('531) teach at column 7, lines 36-41 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of a organ or tissue cells may be accomplished by one of two

methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells). The argument is therefore not convincing.

32. Arguments presented in Paper No. 11 at page 7 assert that regarding instant claim 8, Nabel et al. ('531) do not teach a polynucleotide-liposome complex that is less negative than the polynucleotide alone because the complex is further modified by adding another compound which increases the negative charge on the polynucleotide-liposome complex.

Nabel et al. ('531) teach at column 9, lines 57-67 "DNA used in the present invention is obtained from suitable cells. The vector is constructed using known techniques to obtain a transformed cell capable of in vivo expression of the therapeutic agent protein. The transformed cell is obtained by contacting a target cell with a RNA or DNA-containing formulation permitting transfer and uptake of the RNA or DNA into the target cell. Such formulations include, for example, retroviruses, plasmids, liposomal formulations, or plasmids complexes with polycationic substances such as poly-L-lysine, DEAE-dextran and targeting ligands." At column 13, lines 1-28, Nabel et al. ('531) goes on to describe a kit for delivery of the polynucleotide. The kit may contain additionally a solution which contains an agent such as poly-L-lysine, polybrene, dextran sulfate or a polycationic material, all of which are stated for the delivery of the DNA containing solution into a blood vessel. These teachings make it clear that Nabel et al. ('531) contemplated the use of polynucleotide-liposome complexes in conjunction

with additional agents such as poly-L-lysine, where poly-L-lysine is known to increase the negative charge on the polynucleotide-liposome complex. Therefore, the arguments are not found convincing.

Claim Rejections - 35 USC § 103

33. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

34. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of US 5,328,470 (Nabel et al., (A)) and US 5,698,531 (Nabel et al., (B)) in view of US 5,026,558 (Hwang).

The claims are drawn to a process for delivering a polynucleotide into an extravascular parenchymal cell of a mammal by inserting the polynucleotide into a mammalian blood vessel in-vivo, increasing the permeability of the blood vessel, passing the polynucleotide in a solution through the blood vessel into the extravascular space, thereby delivering the polynucleotide into the extravascular parenchymal cell, and then expressing the polynucleotide. The permeability of the blood vessel is increased with pressure against the blood vessel walls, which may be done by increasing the volume of the fluid in the blood vessel. The time of residence of the

polynucleotide-containing solution in the blood vessel and pressure are variable. Various tissues may be treated by this process, including the liver (hepatocytes). Instant claim 8 recites that the polynucleotide alone has a more negative zeta potential than a polynucleotide-compound complex. The blood vessel may be a tail vein as recited in claims 6 and 14. The volume of the solution my be at least milliliter, claim 16. The pressure in the extravascular parenchymal space may be at least 10 mm mercury, claim 18.

Each of Nabel et al., ('470) and Nabel et al., ('531) teach the invention as described above in the rejection under 35 USC 102. Each of Nabel et al., ('470) and Nabel et al., ('531) teach the delivery of the polynucleotide to the blood vessel with a catheter, applying pressure to the solution in the catheter to force the polynucleotide out of the blood vessel into the parenchymal space.

Each of Nabel et al., ('470) and Nabel et al., ('531) did not teach the blood vessel may be a tail vein, nor that the volume of the solution may be at least one milliliter, nor that the pressure in the extravascular parenchymal space may be at least 10 mm mercury.

Hwang teaches at example 2, the delivery of a polynucleotide by injection into a tail vein, and also to a blood vessel with a catheter, for transfecting the parenchymal cells of the liver.

The limitations of instant claim 16, delivery solution volume of at least one milliliter, and instant claim 18, the pressure in the extravascular parenchymal space may be at least 10 mm mercury, are routine parameters which are well known to those of skill in the art, and in the

absence of unexpected results, do not provide patentable distinction for the instant claimed invention.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the process for delivering a polynucleotide into an extravascular parenchymal cell of a mammal by inserting the polynucleotide into a mammalian blood vessel in-vivo, increasing the permeability of the blood vessel, passing the polynucleotide in a solution through the blood vessel into the extravascular space, thereby delivering the polynucleotide into an extravascular parenchymal cell, and then expressing the polynucleotide as taught in each of Nabel et al., ('470) and Nabel et al., ('531) with the delivery of a polynucleotide by injection into a tail vein, and also to a blood vessel with a catheter, for transfecting the parenchymal cells of the liver as taught by Hwang to produce the instant claimed invention. One of ordinary skill in the art would have been motivated to combine the teachings of Nabel et al., ('470) and Nabel et al., ('531) with Hwang for the expected benefit of delivery of a polynucleotide to a parenchymal cell via a blood vessel by injection into a tail vein which obviates the need for the invasive procedure of using a catheter which is inserted into a blood vessel. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Nabel et al., ('470) and Nabel et al., ('531) who demonstrate the delivery of a polynucleotide to an extravascular parenchymal cell by increasing the permeability of the blood vessel, and Hwang who demonstrates the delivery of a polynucleotide by injection into a tail vein for transfecting the parenchymal cells of the liver.

Response to Arguments

35. Arguments presented in Paper No. 11 at page 8 assert that Nabel et al., ('470) and Nabel et al., ('531) do not provide enabling guidance on delivery of a polynucleotide using increased pressure to a cell other than a vascular cell.

Nabel et al. ('470) teach at column 5, lines 14-16 "vector DNA may be delivered to a large amount of parenchymal tissue distributed through the capillary circulation." Nabel et al. ('470) teach at column 7, lines 36-41 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of a organ or tissue cells may be accomplished by one of two methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells).

Nabel et al. ('531) teach at column 4, lines 16-18 "vector DNA may be delivered to a large amount of parenchymal tissue distributed through the capillary circulation." Nabel et al. ('531) teach at column 7, lines 36-41 "[i]t is also possible to transform cells within an organ or tissue. Direct transformation of a organ or tissue cells may be accomplished by one of two methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue." This teaching is explicit and clear that the nucleic acid is delivered to cells outside of a blood vessel (non-vascular cells). The argument is therefore not convincing.

36. Arguments presented in Paper No. 11 at page 8 assert that Hwang teaches small unilamellar vesicles that have a neutral charge, composed of neutral lipids and have a circulation time of 5 hours or more. It is further asserted that because of the high negative charge of nucleic acid, cationic lipids must be used to interact with nucleic acid. Cationic lipids do not form liposomes that have extended stability in serum or prolonged circulation times. It is asserted that the liposomes used by Hwang are incompatible with nucleic acid delivery, and it is therefore not obvious to combine the delivery of neutral liposome to a tail vein as taught by Hwang with the teachings of Nabel et al., ('470) and Nabel et al., ('531).

Hwang teaches at column 3, line 59 - column 4, line 5 "liposomes under this dual-pathway control of uptake have several characteristics....[t]hey are small....[t]hey resist rapid phagocytic uptake....[p]referably, such liposomes are unilamellar and neutral in composition, although liposomes composed of positively-charged or negatively charged liposomes can also be used." It is clear from this passage, that Hwang contemplated use of positively charged (cationic) liposomes.

Hwang teaches at column 4, lines 14-34 "[t]he substance to be selectively targeted is incorporated into carrier liposomes....[p]referably, the substance is hydrophilic....the substance can be a polypeptide....[t]he substance can also be a polynucleotide, such as a segment of a DNA carrying the gene for a particular known function". It is clear from this passage that Hwang contemplated the use of liposomes to carry DNA.

Hwang teaches at the abstract "[a]n improved method for selectively targeting a substance either to parenchymal cells or the non-parenchymal cells of the liver makes use of the property that there are two pathways for uptake of liposomes by the liver". Hwang also teaches at the abstract that the liposomes are to be delivered to the circulation (blood vessels) of an animal. Hwang makes it clear from these statements, that the method of Hwang is useful for delivery of liposomes to parenchymal cells in an animal. The liposomes are delivered to parenchymal cells in the animal by way of the circulation (blood vessels). The liposomes may contain DNA which carries a gene. The liposomes may be composed of positively charged (cationic) liposomes. Therefore, the argument is not found convincing.

Conclusion

37. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

38. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO

DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
July 8, 2003

JAMES KETTER
PRIMARY EXAMINER